REMARKS/ARGUMENTS

Claims 1, 3, 5, 11, 15, 16 and 40-42 are active in this application.

Claim 42 has been amended to depend only from Claims 1 or 3 and therefore should be rejoined to the elected subject matter. Claim 39 has been cancelled due to the restriction imposed by the Office.

The remaining amendments are for clarity and do not introduce new matter.

In view of the amendments and the following remarks, Applicants request reconsideration and allowance of all pending claims.

The rejection of Claims 1, 3, 5, 11, 15, 16, 40 and 41 under 35 U.S.C. 112, first paragraph ("enablement") is respectfully traversed.

As alleged support for this rejection, the Office contends that the specification 1) does not teach how to effectively modulate any immune response, and 2) the compounds of this invention are not the compounds used in the prior art . This position appears to be based on the lack of a working example in the specification and the belief that practicing the invention would require undue experimentation. Applicants disagree.

While there is no working examples in the specification, there is sufficient guidance in the specification and in the art that provide the necessary knowledge for using the claimed methods to effectively modulate an immune response. For example, one need only perform the systemic administration of a peptide composition in a dose range between 5 and 50 mg of peptides per kg of body weight as disclosed in Bouchon et al., *Nature* 410:1103, 2001, and Gibot et al., J Exp Med. 200:1419, 2004, (each previously made of record) as recited in the claims to effectively modulate an immune response. In addition, operability of the claimed methods can be predicted by analogy to the art of Bouchon et al. and Gibot et al.

The Examiner's allegation that undue experimentation would be required to practice the claimed invention based on the perception that there is dissimilarities between the compounds of this invention and those in the art is misplaced. The fact is that there is a relationship between the structure of the TREM-1 molecules that are members of the Ig superfamily and their respective biological activity. In biology, molecules are described by their respective biological activity. In the case of cellular receptors, their respective biological activity relates to their binding sites. The specificity of TREM-1 is that it is a member of the Ig superfamily of cellular receptors as demonstrated by Kelker et al. *J. Mol. Biol.* 342:1237, 2004 and Ibid. *J. Mol. Biol.* 344:1175, 2004 (of record). The members of this Ig family are characterized by having loop domains folding on each others. It has been extensively demonstrated over the last three decades that the binding activity of these Ig superfamily receptor molecules is effected by the binding sites located in these disulfide bounded loop domains (see chapter 16 p. 427-29 of Immunology by H. N. Eisen and see Chapter 7 pp. 7.1 -7.3 of Immunology by I. M. Roitt et al, copies attached). Although, the work of Kelker et al. could not identify specifically the exact sequence of the binding site in the loop domain as pointed out by the Examiner, the work of Kelker et al. has confirmed the structure and presence of these loops domains in the different TREM-1 molecules studied. Therefore, the scientific evidence points out that the binding site activity of TREM-1 is within its the loop domain as described in figures 1, 4 and 5 of the present application because of its overall structure and its appertaining to the Ig superfamily of receptors. As cited by Kelker et al. *J. Mol. Biol.* 342:1237, 2004 " TREM-1 (Figure 2(a) and (b), cyan) maintains an overall structure that is homologous to other members of the Ig family," (see page 1240) and " Comparison of the TREM-1 structure to other members of the Ig-V Type fold demonstrates a close structural relationship." (see page 1239)

It should be noted that the statement from Kelker et al cited by the Examiner is given improper weight because it is irrelevant to the whole demonstration of the articles showing a close structural relationship between the Ig-V fold and the TREM-1 structure (i.e. the characteristic presence of the loop domain inside of which the binding site is located). As explained in Applicants' response of September 2005, TREM-1sv has the exact same sequence of the extracellular domain of TREM-1 or the TREM-1/IG1 described in Bouchon et al. Moreover, Gibot et al. obtained effective immune modulation activity with a small peptide containing only a part of the sequence loop domain. Thus, compounds having a portion (Gibot et al.), the whole portion,or more than the whole portion (Bouchon et al.) of amino acids 36-114 of SEQ ID NO:2 all have a degree of effective immune modulation activity because they contain part of or the whole binding activity site.

As to how to define the dosage, this is routine in the field and certainly cannot be the basis to allege undue experimentation. As mentioned earlier, one can perform the systemic administration of a peptide composition in a dose range between 5 and 50 mg of peptides per kg of body weight as disclosed in Bouchon et al. and Gibot et al as recited in the claims to effectively modulate an immune response. Moreover, as the claimed methods here relate to a therapeutic method some degree of individual variation among patients is inevitable. Medical practitioners routinely prescribe a dose of a therapeutic agent to a patient, observe the response (including any side effects), and modify the dosage or identity of the therapeutic agent depending on the individual patient's response.

Taken together then, the specification coupled with the knowledge in the field demonstrates the biological activity of immune modulation of all the compounds claimed. Withdrawal of this rejection is requested.

The rejections of Claims 1, 3, 5, 11, 15, 16, 40 and 41 under 35 U.S.C. 102 (e) in view of US Patent 6,420,526 or US Patent 6,504,010 are respectfully traversed. .

A basis of the rejection is the apparent n similarity of the sequence SEQ ID NO: 1825 and SEQ ID NO: 2 of this application. US '010 describes a hypothetical therapeutic method to treat lung cancer. The mechanism of action is unclear and no proof or evidence of such a lung cancer therapy using SEQ ID NO 1825 is presented in US '010 because such therapeutic effect is simply non existent and is against current understanding of how SEQ ID NO 1825 can act biologically. There is a proposed targeted mechanism of T cell activation but there is no scientific logic to support it. The reason is that as previously described in Applicants' response of 12 September 2005, TREM-1 is a receptor present on macrophages and myeloid cells and although activation of macrophages could lead to activation of T cells, such activation cannot be anticipated by the use of TREM-1sv or SEQ ID NO 1825 since they are inhibitors of macrophage activation and not stimulators. US '010 describes to **activation** of the immune system and **not to a reduction** of activation such as in the present application. Consequently, there is no guidance referring to the method claimed in this application and thus no description or suggestion for down regulatimg the immune response. In other words, US '010 proposes hypothetically to treat cancer and in order to treat cancer one would need to activate the TREM-1 receptor, **not** reduce its activity. The use of TREM-1sv or SEQ ID NO 1825 reduces the TREM-1 receptor activity and as a result, the immune response. It is illogical that the claimed therapeutic method is anticipated by US '010 because, US '010 describe the opposite effect of what is being claimed.

Similarly, the rejection based on US '526 due to an alleged inherent property of SEQ ID NO 478. It is well-established law that in order for a reference to anticipate a claimed invention, the reference or references must provide an enabling disclosure sufficient to place

the public in possession of the claimed invention.[1] Likewise, this analysis extends to obviousness, where a holding of obviousness cannot be sustained "unless there is some known or obvious way to make the thing or to carry out the process."[2]

Fundamentally, US '526 lacks any real disclosure that would put into the public's possession the claimed methods. US '526 merely describes an EST DNA sequence, among many others, including a matching sequence of TREM-1sv. US '526 does not indicate which one or which combination of the sequence SEQ ID NO 478 being presented in seven different epitopes, must be used to produce a polypeptide usable as a protein therapeutic to modulate an immune response and whether it is an up-modulation or a down-modulation. Consequently, how can one anticipate a complete therapeutic method from such a lack of information unless it refers to the present invention? The present invention fulfills the need by clearly defining the use of TREM-1sv as a protein therapeutic for down-regulating the immune response.

Applicants respectfully request that both grounds of rejection be withdrawn.

The new matter rejection under 35 U.S.C. § 112, first paragraph is respectfully traversed because the claims are supported by the specification.

The examiner asserts that the new claims represent a departure from the application as originally filed by missing a clear support for " a composition comprising at least a portion of amino acid 1 to 136..." and having support only for variant of TREM-1.

---

[1]See MPEP 2121.01 and *In re Hoeksema*, 399 F.2d 269, 158 USPQ 596 (CCPA 1968).

[2]See *In re Collins*, 462 F.2d 538, 174 USPQ 333 (CCPA 1972), citing *In re Hoeksema*, see *supra*.

The objection raised by the Examiner regarding the term "comprising" has been taken into consideration and the Applicant has complied by amend the claims to remove this term before the polypeptide.

Support for the phrase in claims 1 and 3 if " any soluble polypeptide having at least a portion of amino acid 36 to 114 of SEQ ID NO:2, the whole portion ... or more than the whole portion..." is presented in great detail in the specification paragraphs 55, 59, 60, 72, 73, 75, 76, 78, 80 in which "...present invention also includes, but is not limited to variants or biological function equivalents of the TREM-1 splice variant..." "...variants and further variants with deletion and or addition in any combination..." are presented and thus referred to in the claims as being "...any soluble polypeptide having at least a portion of amino acid 36 to 114 of SEQ ID NO:2, the whole portion ... or more than the whole portion...".

Applicants respectfully request that the rejection be withdrawn.

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to pass this application to allowance.

Respectfully submitted,

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6 THE GENERATION OF DIVERSITY

Dr Frank Hay

7 ANTIGEN RECOGNITION

Professor Michael Steward

8 CELL COOPERATION IN THE IMMUNE RESPONSE

Professor Marc Feldmann and Dr David Male

9 CELL-MEDIATED IMMUNE RESPONSES

Dr Graham Rook

7 Antigen Recognition

Antibody and the T cell antigen receptor have many features in common. They both have variable (V) and constant (C) domains, and the process of gene recombination which produces the variable domains from V, D and J gene segments is also similar for each type of receptor. Nevertheless the ways in which B cells and T cells recognize antigen is quite different: antibody recognizes antigens in solution or on cell surfaces in their native conformation, while the T cell receptor sees antigen in association with MHC molecules on cell surfaces. Frequently, antigens recognized by T cells are degraded or processed in some way, so that the determinant recognized by the T cell antigen receptor is only a small fragment of the original antigen.

Another difference between antibody and the T cell antigen receptor is that antibody may be produced in two forms, either as the B cell antigen receptor or as secreted antibody, whereas the T cell antigen receptor is an integral membrane protein. Secreted antibody is essentially a bifunctional molecule in which the V domains are primarily concerned with antigen binding and the C domains interact with receptors on host tissues.

This chapter describes the ways in which the V domains of antibody and the T cell antigen receptor form an antigen binding site and how they then interact with their specific antigens or antigen/MHC. These interactions underlie the specificity of the adaptive immune response.

ANTIGEN–ANTIBODY BINDING

X-ray crystallography of antibody V domains shows that the hypervariable regions are clustered at the end of the Fab arms, and it is particular residues in these regions which interact specifically with antigen (Fig. 7.1). The framework residues do not usually form bonds with the antigen but are essential for producing the folding of the V domains and maintaining the integrity of the binding site.

The binding of antigen to antibody takes place by the formation of multiple non-covalent bonds between the antigen and amino acids of the binding site. Although the attractive forces (namely, hydrogen bonds, electrostatic, Van der Waals and hydrophobic) involved in these bonds are individually weak by comparison with covalent bonds, the multiplicity of the bonds leads to a considerable binding energy.

The non-covalent bonds are critically dependent on the distance (d) between the interacting groups. The force is proportional to $1/d^2$ for electrostatic forces and to $1/d^7$ for Van der Waals forces; thus the interacting groups must be close in molecular terms before these forces become significant (Fig. 7.2). The consequence of this is

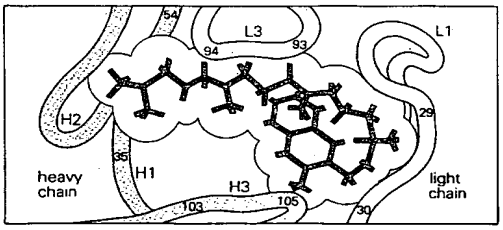


Fig. 7.1 The antibody combining site. The antigen molecule nestles in a cleft formed by the antibody combining site. The example shown is based on X-ray crystallography studies of human IgG (the myeloma protein NEW) binding γ-hydroxyl vitamin K. The antigen makes contact with 10–12 amino acids in the hypervariable regions of both heavy and light chains. The numerals refer to amino acids identified as actually making contact with the antigen.

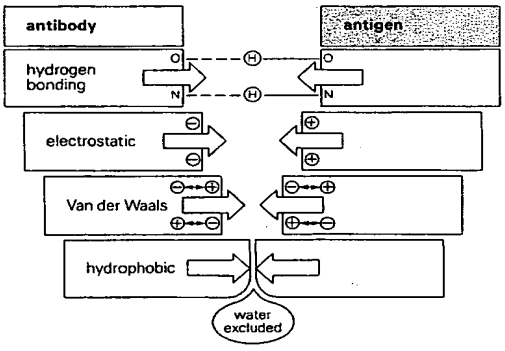


Fig. 7.2 The intermolecular attractive forces binding antigen to antibody. These forces require the close approach of the interacting groups.
Hydrogen bonding results from the formation of hydrogen bridges between appropriate atoms.
Electrostatic forces are due to the attraction of oppositely charged groups located on two protein side chains.
Van der Waals bonds are generated by the interaction between electron clouds (here represented as induced oscillating dipoles).
Hydrophobic bonds (which may contribute up to half the total strength of the antigen–antibody bond) rely upon the association of non-polar, hydrophobic groups so that contact with water molecules is minimized.
The distance of separation between the interacting groups which produces optimum binding varies for the different types of bond.

that an antigenic determinant and the antigen combining site must have complementary structures to be able to combine, meaning that:

1. there must be suitable atomic groupings on opposing parts of the antigen and antibody
2. the shape of the combining site must fit the antigen, so that several non-covalent bonds can form simultaneously.

If the antigen and the combining site are complementary in this way, there will be sufficient binding energy to resist thermodynamic disruption of the bond. However, if electron clouds of the antigen and antibody overlap, steric repulsive forces come into play which are inversely proportional to the twelfth power of the distance between the clouds ($F \alpha 1/d^{12}$). These forces play a vital role in determining the specificity of the antibody molecule for a particular antigen and its ability to discriminate between antigens, since any variation from the ideal complementary shape will cause a fall in the total binding energy through increased repulsive forces and decreased attractive forces. Examples of a good fit and a poor fit between antigen and antibody are illustrated in Fig. 7.3.

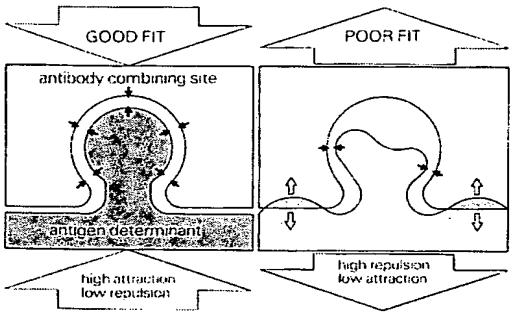


Fig. 7.3 Good fit and poor fit between antigen and antibody. A good fit between the antigenic determinant and the binding site of the antibody will create ample opportunities for intermolecular attractive forces to be created and few opportunities for repulsive forces to operate. Conversely, when there is a poor fit the reverse is true, that is, when electron clouds overlap high repulsive forces are generated, which dominate any small forces of attraction.

Recent studies have shown how protein antigens interact with specific antibodies. For example, an examination of the interaction between the antigen lysozyme and the Fab of an antibody to lysozyme shows that the antigen epitope and the binding site have complementary surfaces and that these extend even beyond the hypervariable regions. In this example, 17 amino acid residues on the antibody were in contact with 16 residues on the antigen (Fig. 7.4). All of the hypervariable regions contributed to the antibody binding site, although the third hypervariable region formed by the VDJ join in the heavy chain gene appeared to be most important. This may be related to the greater variability generated by recombination of the V, D, and J segments.

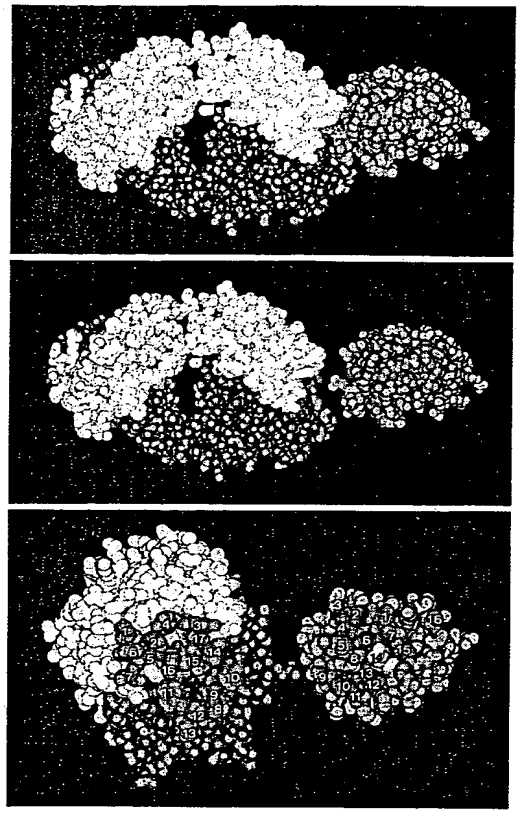


Fig. 7.4 The Fab–lysozyme complex. The upper figure shows lysozyme (green) binding to the hypervariable regions of the heavy (blue) and light (yellow) chains of the Fab fragment of antibody DI.3. The centre panel shows the complex separated with Glu 121 (red) visible. This residue fits into the centre of the cleft between the heavy and light chains. The lower panel shows the molecules rotated forward 90° to show the contact residues which contribute to the antigen–antibody bond. (Courtesy of Dr R.J. Poljak; permission from *Science* 1986, **233**, 747–753. Copyright 1986 by the AAAS.)

ANTIBODY AFFINITY

The strength of a single antigen–antibody bond is the antibody affinity; it is produced by summation of the attractive and repulsive forces described above (Fig. 7.5). Interaction of the antibody combining site with antigen can be investigated thermodynamically. To measure the affinity of a single combining site it is necessary to use a monovalent antigen or even a single isolated antigenic determinant – a hapten. Since the non-covalent bonds between antibody and hapten are dissociable, the overall combination of an antigen and antibody must also be reversible; thus the Law of Mass

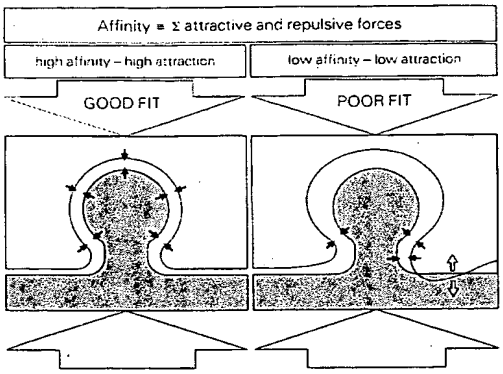


Fig. 7.5 Antibody affinity. The affinity with which antibody binds antigen results from a balance between the attractive and repulsive forces. A high affinity antibody implies a good fit and conversely, a low affinity antibody implies a poor fit.

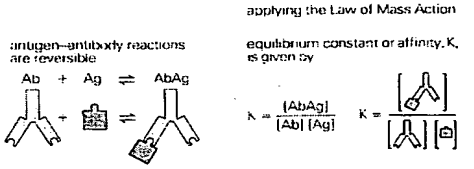


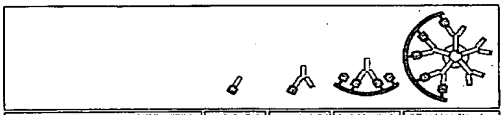
Fig. 7.6 Reversibility of the antigen–antibody bond and the calculation of antibody affinity. All antigen–antibody reactions are reversible and the Law of Mass Action has been applied, from which antibody affinity (given by the equilibrium constant, K) can be calculated at equilibrium. (Square brackets refer to the concentration of the reactants.)

Action can be applied to the reaction and the equilibrium constant, K, can be determined. This is the affinity constant (Fig. 7.6).

AFFINITY AND AVIDITY

Since each antibody unit of four polypeptide chains has two antigen binding sites, antibodies are potentially multivalent in their reaction with antigen. In addition, antigen can also be monovalent or multivalent. A hapten has only one antigenic determinant and can therefore react with only one antigen combining site; thus it is monovalent. Many molecules however, have more than one antigenic determinant. Microorganisms have a large number of antigenic determinants exposed on their surfaces, hence they are all multivalent. When a multivalent antigen combines with more than one of an antibody's combining sites, the binding energy between the two is considerably greater than the sum of the binding energies of the individual sites since all the antigen–antibody bonds must be broken simultaneously before the antigen and antibody dissociate.

The strength with which a multivalent antibody binds a multivalent antigen is termed avidity, to differentiate it from the affinity of the bond between a single antigenic determinant and an individual combining site. Thus, the avidity of an antibody for its antigen is dependent on the affinities of the individual combining sites for the determinants on the antigen, but is greater than the sum of these affinities if both antigen and antibody are multivalent (Fig. 7.7). In normal physiological situations avidity is likely to be more relevant than affinity since naturally occurring antigens are multivalent; however, the precise measurement of hapten–antibody reactions is more likely to give an insight into the immunochemical nature of the antigen–antibody reaction.



antibody	Fab	IgG	IgG	IgM
effective antibody valence	1	1	2	up to 10
antigen valence	1	1	n	n
equilibrium constant (L/M)	10^4	10^4	10^7	10^{11}
advantage of multivalence	–	–	10^3-fold	10^7-fold
definition of binding	affinity	affinity	avidity	avidity
	intrinsic affinity		functional affinity	

Fig. 7.7 Affinity and avidity. Multivalent binding between antibody and antigen (avidity or functional affinity) results in a considerable increase in stability as measured by the equilibrium constant, compared to simple monovalent binding (affinity or intrinsic affinity, here arbitrarily assigned a value of 10^4 L/M). This is sometimes referred to as the 'bonus effect' of multivalency. Thus there may be a 10^3-fold increase in the binding energy of IgG when both valencies (combining sites) are utilized, and a 10^7-fold increase when IgM binds antigen in a multivalent manner.

ANTIBODY SPECIFICITY

Antigen–antibody reactions can show a high level of specificity. For example, antibodies to a virus like measles will bind to the measles virus and confer immunity to this disease, but will not combine with, or protect against, an unrelated virus such as polio. The specificity of an antiserum is the result of the summation of the actions of the various antibodies in the total population each reacting with a different part of the antigen molecule and even different parts of the same determinant (Fig. 7.8). However, when some of the determinants of an antigen, A, are shared by another antigen, B, then a proportion of the antibodies directed to A will also react with B. This phenomenon is termed cross-reactivity. The specificity and cross-reactivity expressed by an antiserum are properties which result from the antibody molecules within the serum.

immunology

AN INTRODUCTION TO MOLECULAR AND CELLULAR PRINCIPLES OF THE IMMUNE RESPONSES

revised reprint

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chapter 16

ANTIBODY STRUCTURE: THE IMMUNOGLOBULINS

)acterial capsular polysaccharides pro-
:d by animals after intensive immunization
streptococcal or pneumococcal vaccines
s. 16-17 and 16-18). In many of these
ıals serum Ab levels of 20 to 50 mg/ml
attained, and the Abs are of **restricted**
rogeneity, i.e., they are separable into two
ıree distinctive, homogeneous Abs.

rare animal may produce a massive amount of
gle Ab, as homogeneous as a myeloma protein,
unlike actual myeloma tumors, production de-
s on continued administration of immunogen.
linical analogy is seen in occasional elderly
ons with a benign form of Waldenström's mac-
)bulinemia who produce, without known im-
ization, two to four monoclonal IgM proteins,
: of which react specifically with bacterial
saccharides. It is possible that these individuals
subjected to prolonged antigenic stimulation by
of their own cryptic microorganisms or per-
: by cross-reacting "self" Ags (see Ch. 17,
:rance; Ch. 20, Autoimmune disease). Ags that
narily elicit highly heterogeneous Abs (such as
-proteins in the production of anti-Dnp Abs)
:ar to elicit Abs of restricted heterogeneity in
nals of certain highly inbred strains, suggesting
genetic control, not just the nature of the Ag,
rmines **clonal dominance,** the ability of one or
a few clones of Ab-forming cells to overgrow others (Ch. 17, Clonal selection).

AMINO ACID SEQUENCES: THE BASIS FOR IMMUNOGLOBULIN DIVERSITY

Since Abs are highly diverse with respect to ligand-binding activities their combining sites must have diverse shapes. How can this variability be reconciled with the limitations imposed by the over-all structural uniformity described above? The cogency of this question is emphasized by the contrast with enzymes of diverse specificities, which are conspicuously dissimilar in structure (Table 16-4). A general answer emerged from analyses of amino acid sequences, which also established a chemical basis for the distinctions among isotypes, allotypes, and idiotypes, and brought into focus fundamental genetic issues underlying the diversity of Abs and their evolutionary development.

Most preparations of purified Abs are mixtures of many kinds of Ig molecules. Accordingly, the most extensive sequences have been established for myeloma and Bence

. **16-17.** Homogeneous antibody (arrow) raised in a rabbit. Serum samples
'e analyzed by electrophoresis on a cellulose acetate membrane. **A.** Before
nunization. **B.** After 16 injections (4 weeks) of streptococcal vaccine (group
the sample had about 40 mg Ab per milliliter serum. **C.** After absorption of
sample in **B** with purified envelope carbohydrate of group C streptococci.
npact, dark bands of serum albumin are at the right. [From Eichmann, K.,
:kland, A., Hood, L., and Krause, R. M. *J Exp Med 131*:207 (1970).]

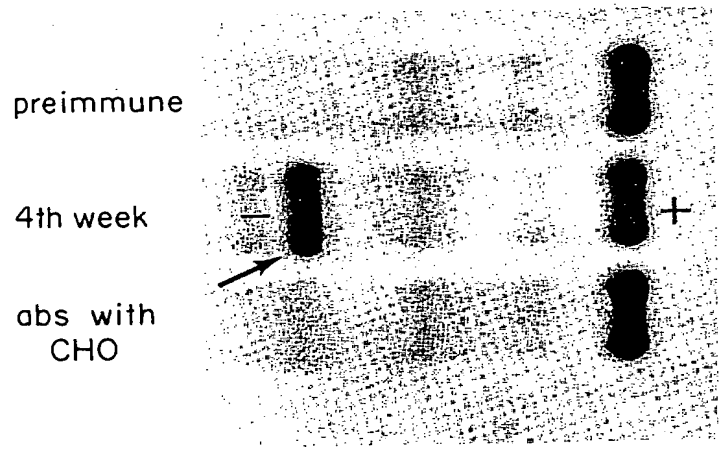


TABLE 16-4. Contrast Between Structural Diversity of Enzymes and Gross Structural Uniformity of Antibodies

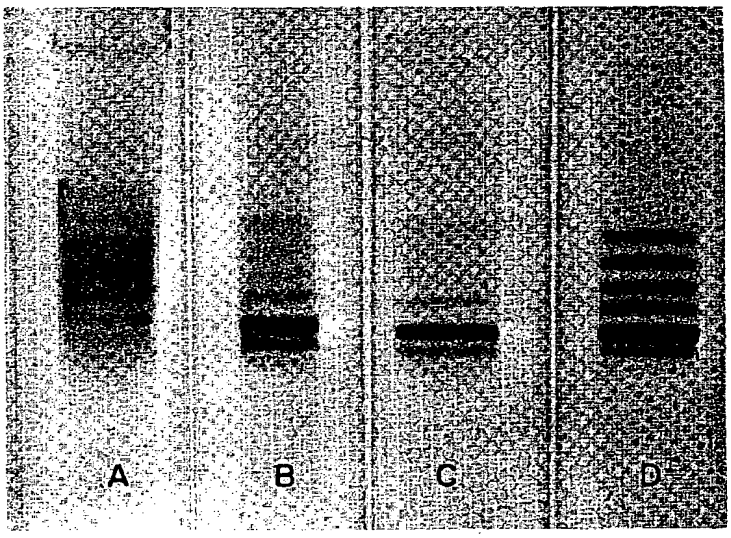
Enzymes	Molecular weight	No. of chains	IgG antibodies specific for	Molecular weight	No. of chains
E. coli alkaline phosphatase	80,000	2	Diphtheria toxin	150,000	4
Pancreatic RNase	13,700	1	Bacteriophage T2	150,000	4
Phosphorylase a	495,000	4	Lysozyme	150,000	4
Yeast enolase	67,000	1	Azophenyl-β-lactoside	150,000	4
Glutamic acid dehydrogenase	336,000	6	2,4-Dinitrophenyl	150,000	4

Jones proteins, which are homogeneous. Similar (but less extensive) sequences have been determined for Igs from normal serum, and especially Abs of restricted heterogeneity [elicited by certain bacterial polysaccharides in outbred rabbits (genetically highly diversified) and by hapten-protein conjugates in inbred strains of guinea pigs].

GENERAL FEATURES OF LIGHT AND HEAVY CHAIN SEQUENCES: DOMAINS

Light chains vary slightly in length (211 t 217 residues). Heavy chains are twice a long: γ and α chains have about 450 residue while μ and ε chains have about 550 residue All chains consist of linearly repeating, simila

Fig. 16-18. Light chains from purified rabbit antibodies to pneumococcal polysaccharide (type 8) examined by polyacrylamide disc electrophoresis. **A.** From a rabbit with heterogeneous (polyclonal) Abs. **B–D.** From a rabbit after the first **(B)**, second **(C)**, and third **(D)** courses of immunization. Virtually homogeneous (monoclonal) Ab was obtained after the second course **(C)**. Bence Jones proteins and light chains from a myeloma protein migrate as one band (or sometimes as two due to presence of a dimeric form of light chain). [From Pincus, J. H., Jaton, J.-C., Bloch, K. J., and Haber, E. *J Immunol 104*:1149 (1970).]



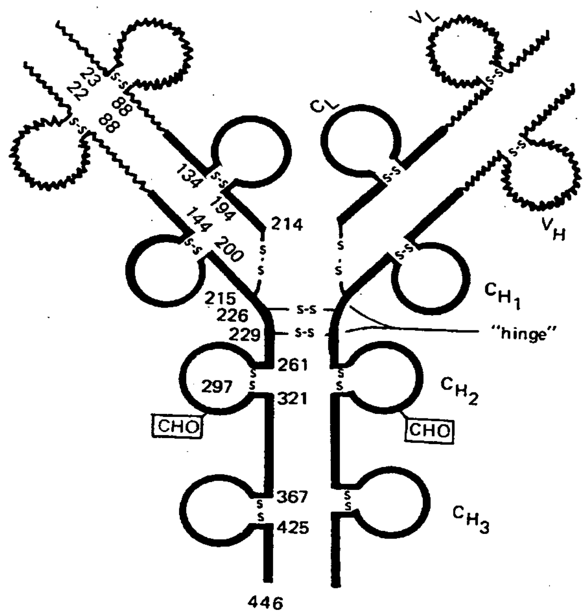


Fig. 16-19. Linear periodicity in amino acid sequences suggests that light (L) and heavy (H) chains have repeating domains, each with about 110 amino acid residues and an approximately 60-membered S-S bonded loop. Domains with variable sequences are represented by jagged lines (V_L, V_H); those with invariant sequences in a given class of H or type of L are represented by smooth lines (C_L, C_{H1}, C_{H2}, C_{H3}; see Fig. 16-21). Numbered positions refer to cysteinyl residues that form S-S bonds, or to the point of attachment of an oligosaccharide (CHO). For other arrangements of interchain S-S bonds see Figure 16-20. [Based on Edelman, G. M. *Biochemistry* 9:3197 (1970).]

(but not identical) segments of about 110 residues: in each segment an S-S bond establishes an approximately 60-membered loop. Similarities in sequence suggest that each segment may be folded into a compact globular **domain,** stabilized by the S-S bond (Fig. 16-19).* Adjacent domains are evidently linked by less tightly folded regions: thus pepsin can cut isolated light chains into halves, just as it cleaves between two heavy chain domains in intact Ig molecules in the production of Fab′ fragments (Fig. 16-5). Light chains contain two such domains, and heavy chains contain four (γ and α chains) or five (μ and ε chains). (Occasional domains have additional, smaller S-S bonded loops.)

Other cysteine residues form the interchain S-S bonds that link chains within molecules. The interchain bonds differ in number and position in different classes and subclasses of heavy chains (Fig. 16-20) and types of light chains; e.g., the light-heavy interchain S-S bond involves a cysteine that is C-terminal in κ chains and penultimate in λ chains (see Fig. 16-23).

* See x-ray diffraction-analysis in Addendum, p. 629.

VARIABLE (V) AND CONSTANT (C) SEGMENTS

The first two Ig chains that were sequenced (human κ chains by Hilschmann and Craig and by Putnam *et al.*) revealed a remarkable pattern that has since been found consistently in all others. The two chains had different amino acid residues at many positions; but, strikingly, the differences were all clustered in the **amino-terminal half** of the chain, now called the variable or V segment or V_κ (Fig. 16-21). In the carboxyl half of the chain, called the constant or C segment (or C_κ), the sequences were identical except at position 191, where leucine and valine occur as

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